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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/249,543 | 02/12/1999 | THOMAS C. EVANS | NEB-154 | 1052 |

28986 7590 03/10/2004

NEW ENGLAND BIOLABS, INC.
32 TOZER ROAD
BEVERLY, MA 01915

| EXAMINER | |
|---|---|
| MOORE, WILLIAM W | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

DATE MAILED: 03/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/249,543 | EVANS ET AL. | |
| | Examiner | Art Unit | |
| | William W. Moore | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *22 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *63-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-89* is/are rejected.

7)☒ Claim(s) *90* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

### *Response to Amendment*

Applicant's Amendment filed August 22, 2003, has been entered, providing a new Sequence Listing, amending the description of Figure 4 at page 7 of the specification, canceling claims 1-62, and adding the new claims 63-90. It was agreed in the Interview conducted August 15, 2003, that recitations of "cysteine or selenocysteine" in claims 65, 73, 74, 80, 82, and 88 do not constitute new matter where selenocysteine is among the "naturally-occurring amino acids" indicated at lines 23 and 24 of page 11 of the specification. The interview conducted August 15, 2003, also resulted in recitations of the term "intramolecular" in terminal clauses of methods now represented by claims 74 and 80 and of the term "intermolecular" in terminal clauses of methods now represented by claims 82 and 88 and it is agreed that such terms do not constitute new matter because they are inherent features of ligation methods using first and second target proteins and cyclization and polymerization methods using a target protein.

### *Claim Objections*

Claim 90 is objected to because of the following informalities: It is disconsonant and incomplete in reciting, "[a] modified . . . intein, the . . . comprise SEQ ID NO:24 and the modification comprising . . ."(emphases supplied), because the preamble's subject is absent from the subsequent phrase and because the subsequent phrase would properly recite the same form of the verb in both instances rather than different forms in either instance. A grammatically consonant recitation would be: "[a] modified . . . **intein**, the . . . **intein comprising** SEQ ID NO:24 and the **modification comprising** . . ." (emphases supplied). An alternate, appropriate, recitation would be: "[a] modified . . . **intein**, wherein the . . . **intein comprises** SEQ ID NO:24 and **the modification comprises** . . ." (emphases supplied). Appropriate correction is required.

*Enablement of Ligation Methods Utilizing Unmodified and Modified Inteins*

Telenti et al., 1997, of record, was discussed in the interview conducted August 15, 2003, with respect to enablement of practice of claimed methods using unmodified, or native, inteins. Telenti et al. disclose, in Table 1 at page 6380, that an unmodified *Mxe* GyrA intein permits either an *in vitro* amino-terminal [N-terminal] or an *in vitro* carboxyl-terminal [C-terminal] cleavage from either flanking fusion partner in a tripartite fusion polypeptide without appreciable, concomitant, formation of a spliced product depending on the temperature of induction and the presence or absence of a thiol reagent, dithiothreitol [DTT], in the *in vitro* induction process. The unmodified intein is no longer in its native context, flanked by the exteins of the microbial gyrase enzyme where it was found, but is in the same context shown in Figure 3 of the instant specification, i.e., flanked by different, exogenous, fusion partners of which one is a binding protein, or binding protein domain, that facilitates purification of a fusion polypeptide. Telenti et al. show that when the native intein is present in the tripartite fusion polypeptide *in vivo*, splicing is the primary reaction that occurs, whether at either 37°C or 16°C, and yields a free intein and a spliced product that comprises both flanking fusion partners.

Telenti et al. further show in Table 1 that lysing the host cell to isolate the tripartite fusion polypeptide, then incubating the lysate *in vitro* with DTT at 16°C, results entirely in N-terminal intein cleavage at the native intein where formation of a stable thioester at the carboxyl terminus of the intein's amino-proximal fusion partner precludes a splicing reaction. Conversely, removing the tripartite fusion polypeptide from the host cell, then incubating it *in vitro* at 16°C without DTT, results primarily in C-terminal intein cleavage at the native intein, 92% of the observed product, rather than formation of a free intein and a spliced product comprising the flanking fusion partners because the presence of heterologous exteins favors cleavage producing a free carboxyl-proximal fusion partner

rather than splicing. Telenti et al. show that including a portion of the N-terminal amino acid sequence of the native extein at the amino terminus the intein's carboxyl-proximal fusion partner permits an improved yield of a C-terminal cleaved product that comprises the intein and its exogenous amino-proximal fusion partner upon incubation of the host cell lysate comprising the tripartite fusion polypeptide at 16°C *in vitro* without a thiol reagent. Telenti et al. also show that amino-terminal modification of a carboxyl-proximal fusion partner only slightly reduces the yield of N-terminal cleaved product comprising the intein and its flanking carboxyl-proximal fusion partner when a lysate comprising the tripartite fusion polypeptide is incubated *in vitro* at 16°C with a thiol reagent.

Additional disclosures of Telenti et al. make it clear that modifying the amino acid sequences of inteins at amino acid positions distant from the N-terminal and C-terminal positions the specification identifies can affect whether, and how, a modified intein can be used to provide the C-terminal and N-terminal cleavage reactions that the methods claimed herein require. The C114R modification that Telenti et al. made in the *Mxe* GyrA intein rendered the intein unsuitable, see Table 1, for splicing as well as for C-terminal and N-terminal cleavage reactions unless the intein's carboxyl-proximal fusion partner was also modified to include a portion of the N-terminal amino acid sequence of the native extein, allowing with this internally-modified intein to support C-terminal and N-terminal intein cleavage reactions when a host cell lysate comprising the tripartite fusion polypeptide is incubated *in vitro* at 16°C with, and without, a thiol reagent.

Where the prior art of record taken together with the disclosure of the specification, e.g., the legend for Figure 3 at page 7 of the specification, suggests how skilled artisans can use native, unmodified, inteins in the ligation methods of claims 65 and 69-73 without undue experimentation, the claimed methods comport with the analysis required by *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the

"*Forman*" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). The specification need not teach that which is well-known in the art and the artisan, reading Telenti et al., would appreciate the circumstances in which a claimed method of ligation could incorporate an unmodified, or native, intein rather than an intein having the modifications disclosed in the specification. Thus the artisan seeking to practice methods of ligation described by the new claims 65-73 requiring separate fusion polypeptides, one comprising a first target protein fused at its carboxyl-terminus to a first intein and the other comprising a second target protein fused at its amino-terminus to a second intein, would know how to modify a native intein at either or both of its amino-terminal and carboxyl-terminal amino acid positions according to the specification, would know how to leave these positions unmodified, would know how to modify the native intein elsewhere within its amino acid sequence such as deleting an unnecessary exonuclease region, and would know how to both modify the intein elsewhere in its amino acid sequence as well as at either or both of its amino-terminal and carboxyl-terminal amino acid positions. Such an artisan would require no undue experimentation to select a temperature of *in vitro* incubation, to select the presence and concentration of, or absence of, a thiol reagent during *in vitro* incubation, as well as to selectively include the amino terminal sequence region that in Nature occurs in the carboxyl-proximal extein flanking the intein at the amino terminus of a second, target, protein of a claimed method, or to exclude such an extein amino terminal sequence region, in order to favor the recovery of a desired, amino-terminal cleaved, target protein as well as a desired carboxyl-terminal cleaved target protein, over recovery of a spliced polypeptide, and such an artisan would know that the relative yields of desired amino-terminal cleaved, or desired carboxyl-terminal cleaved, target proteins over spliced products may be increased by manipulating such conditions.

*Double Patenting*

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

New claim 73 necessitates this provisional rejection under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22-25 and 27-30 of copending Application No. 09/786,009 because the new claim 73 recites, "[a] method for ligating a first and a second target protein comprising (a) combining in a mixture (i) a first target protein having a C-terminus . . . compris[ing] a thioester formed by cleavage of a first intein or modification thereof from a first fusion protein . . . . and (ii) a second target protein having an N-terminus, wherein the N-terminus is a cysteine or selenocysteine amino acid, the N-termin[al] cysteine or selenocysteine resulting from induced cleavage of a second intein or modification thereof in a second fusion protein. . . and (b) ligating the first and second target proteins" (underlined for emphasis). Although the conflicting claims are not identical, they are not patentably distinct from each other where the product-by-process description of a second target protein in clause (a)(ii) of claim 73 in the copending application admits the use of a product made by another process. A product of clause (a)(i) of claim 73 of the copending application is also the first target protein of claims 22-25 and 27-30 herein, the process of ligation of claim 73 of the copending application is also the process of ligation of claims 22-25 and 27-30 herein, and a product that "result[s] from" a process of clause (a)(ii) of claim 73 of

the copending application does not differ in structure from products that may result from synthetic processes of claims 22-25 and 27-30 herein, thus the method recited in claim 73 of the copending application embraces methods of claims 22-25 and 27-30 herein. This is a provisional obviousness-type double patenting rejection because the conflicting claim has not in fact been patented.

New claim 73 also necessitates a rejection under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 96 of U.S. Patent No. 5,834,247, of record. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method for ligating a first and a second target protein of claim 73 herein is embraced by claim 96 of the issued patent where the "second target protein having an N-terminus", that may be a "cysteine" of clause (a)(ii) of claim 73, is described in this clause as the "result[ ]" of a process, i.e., as a product-by-process, thus is indistinguishable from a "second" protein product of clause (f) of the patented claim 96 "having an amino terminal cysteine". A patent issuing on the instant application with the present claim 73 would thus constitute an undue extension of the term of the issued patent. It is noted that this rejection may be avoided by deleting the passive, product-by-process, recitation of clause (a)(ii) of claim 73 and recasting the claim to positively require the active expression of a second target protein comprised by an intein-second target fusion polypeptide and to positively require the active cleavage of the second target from the intein, as in clauses (b) and (e) of claim 65 not subject to this rejection.

New claims 65 and 69-73 necessitate a rejection under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 56, 57, 59 and 60 of U.S. Patent No. 5,834,247. Although the conflicting claims are not identical, they are not patentably distinct from each other because methods for ligating

more than one target protein of claims 65 and 69-73 herein are embraced by claims 56, 57, 59 and 60 of the issued patent. First, claim 65 herein permits the use of modified inteins but makes no distinction between modifications which are terminal truncations of an intein described by the issued patent and the terminal amino acid sequence modifications described in the instant application. Methods of both the patented claims and the claims pending herein produce intermediate products that are separate fusion proteins which, after separate intein cleavages, become a ligated protein where claims 69-72 herein state further elements that implement clauses (c) and (d) of claim 65 to provide for separate intein cleavage events. Thus the methods of claims 65 and 69-72 fall within the broad embrace of clause (c) of the patented claim 56 wherein a ligated "target protein" of the patented claims' preamble results from the exposure of separate fusion polypeptides of clauses (a) and (b) of the patented claim to "a condition suitable **for cleavage** of the controllable intervening protein sequence (i.e., an intein) in trans" (emphasis supplied). The recitation, "**cleavage** . . . in trans" in the patented claim 56 describes an event indistinguishable from methods of claims 65 and 69-73 herein where two fusion proteins are separately cleaved, i.e., cleaved in trans.

Similarly, the method of claim 73 herein of ligating different target proteins permits the use of modified inteins but makes no distinction between modifications which are terminal truncations of an intein described by the issued patent and the terminal amino acid sequence modifications described in the instant application. The method of claim 73 herein also generates different, intermediate, target proteins after separate intein cleavages, bringing the method of claim 73 herein within the broad embrace of clause (c) of the patented claim 56 wherein a ligated "target protein" of the preamble results from exposing fusion polypeptides of clauses (a) and (b) of the patented claim to "a condition suitable **for cleavage** of the controllable intervening protein sequence in

trans" (emphasis supplied). The recitation, "**cleavage** . . . in trans" in the patented claim 56 describes an event indistinguishable from methods of claims 65 and 69-73 herein where two fusion proteins are separately cleaved, i.e., cleaved in trans.

New claims 66 and 67 necessitate a rejection under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 56, 57, 59 and 60 of U.S. Patent No. 5,834,247, of record, in view of Smith et al., 1997. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method for ligating a first and a second target protein of claim 65 herein is embraced by claim 56 of the issued patent where methods of claims 66 and 67 herein "for ligating" at least two proteins are obvious species of the patented claim in view of the teaching of the *Mth* R1R1 intein depicted in Figure 8 of the November 1997 publication of Smith et al. because it would have been obvious to one of ordinary skill in the art at the time the invention was made that the specific, *Mth* R1R1 intein, of Smith et al. is among the generic inteins of the patented claim, particularly when such an artisan at that time would have been motivated to use an *Mth* R1R1 intein of Smith et al. in view of the teaching of the issued patent, see col. 3, lines 25-33, that "reducing the overall size of the expressed [fusion polypeptide]" is "valuable" and the teaching of Smith et al. that the *Mth* R1R1 intein was the smallest intein yet known but has the necessary terminal regions to be split into two intein portions, each modified by truncations at opposite termini, where such terminal truncations of an intein described by the issued patent are intein modifications just as the terminal amino acid sequence modifications of the instant application are intein modifications.

*Claim Rejections - 35 USC § 112*

**The following is a quotation of the first paragraph of 35 U.S.C. § 112:**

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**Claims 63, 64 and 89 are rejected, and claim 81 is for reasons of record rejected, under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.**

Claims 63, 64 and 89 submitted August 22, 2003, necessitate new grounds of rejection herein because previously presented claims had not stated methods described by new claims 63 and 64 or a product described by new claim 89. Claim 81 requires a restatement of the rejection of record of claim 21 which had described essentially the same product. Neither of claims 63 and 64 are drawn to subject matter described by the originally-presented claims nor the subject matter of claim 58 of Amendment D filed June 27, 2002, and the specification does not support, e.g., at pages 2-4, 8, 9, 11, 12, 18 and 19, claim 63's negative limitation, "specified amino acid **other than methionine** at the N-terminus" (emphasis supplied), a recitation embraced by claim 64 dependent thereon. As noted in the rejection of record of claim 21, the specification does not describe the preparation of a cyclic fusion protein of claim 81. While the specification exemplifies fusion proteins made by methods of claims 65-73, it does not exemplify a cyclic protein of claim 81 inherently consisting of naturally-occurring amino acids linked exclusively by native peptide bonds. The specification also fails to provide any way to distinguish both a naturally-occurring cyclic proteins consisting of naturally-occurring amino acids linked exclusively by native peptide bonds and a cyclic protein consisting of naturally-occurring amino acids linked exclusively by native peptide bonds produced by a prior art solid-phase synthesis method such as that of Albericio et al., made of record herewith, from a claimed cyclic protein consisting of naturally-occurring amino acids linked exclusively by native peptide bonds produced by cleaving flanking inteins from a target protein in a fusion polypeptide.

The specification also fails to exemplify or demonstrate the preparation of polymeric proteins of claim 89 inherently consisting entirely of naturally-occurring amino acids linked exclusively by native peptide bonds, just as it fails to provide a way to distinguish both a naturally-occurring polymeric protein consisting of naturally-occurring amino acids linked exclusively by native peptide bonds, e.g., a fragment of silk fibroin, and a polymeric protein consisting of naturally-occurring amino acids linked exclusively by native peptide bonds produced by another method, such as a combination the methods of Albericio et al. and Stevens, made of record herewith, from polymeric proteins produced by cleaving flanking inteins from a target protein in a fusion polypeptide. The specification cannot describe products of claims 81 and 89 with such "relevant identifying characteristic[s]" that the public could know Applicant possessed the invention at the time provisional application priority document was filed, other than by a mere "result that one might achieve if one had made that invention". *University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

**Claims 65-72 and 82-89 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for methods of claims 67-72 of ligating a first target protein or peptide with a second, different, target protein or peptide, is not enabling for methods of ligating a "plurality" of target proteins or peptides to form a product comprising only two target proteins. Neither is the specification enabling for methods of polymerizing a "plurality" of heterologous target proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, make and use the invention commensurate in scope with these claims.**

This new ground of rejection is necessitated by the unfortunate choice of the term "plurality of" in the preambles of claims 65, 82 and 88 where methods of claims 65-72 and 82-88 contemplate inclusion of more target proteins in a claimed process than the final product of a claimed processes can comprise and claim 89 contemplates a product made by a method of claim 82. Use of "plurality" in the preambles of claims 65, 82 and 88 connotes inclusion in a claimed method of "more than one of more of one kind or

class" [Webster's Ninth New Collegiate Dictionary, 1990] where the class in the context of the instant specification comprises polypeptides and peptides generally. But clauses (a)-(f) of claim 65 refer only to a first and a second target protein, clause (a) of claim 82 refers only to "a target protein", and the clause following the preamble of claim 88 also refers only to "a target protein". The specification does not teach how to practice a method using more than two starting proteins intended for ligation in making a ligated product comprising only a first and second starting product yet excluding a third, fourth, or further, starting protein. Neither does it teach how to practice methods using multiple starting proteins intended for heteropolymerization in making a heteropolymeric product comprising a first target protein product as well as second, third, fourth, or further, target proteins. The prior art of record herein likewise does not suggest how a third, fourth, or further, starting protein might be excluded from a ligated product comprising two starting proteins in the practice of a method of claims 65-72, nor does it suggest how to include a second, third, fourth, or further, protein with a first target protein in the practice of a method of claims 82-88, or achieve the production of a polymeric protein of claim 89.

It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "*Forman*" factors). Cf., *Ex parte Forman*, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). Because the prior art of record taken together with the disclosure of the specification does not suggest how a result described by the claims might be achieved the state of the art and the level of skill in the art cannot compensate for the lack of

teaching in the instant specification for the practice of methods recited by claims 65-72 and 82-88, or for achieving a product of claim 89.

**Claims 74, 76-82, and 86-89 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for methods of preparing a cyclic protein or peptide as well as preparing a polymeric protein, wherein both a cyclization method and a polymerization method utilize fusion polypeptides comprising a target protein fused to an amino-proximal intein modified to be incapable of splicing and further fused to a carboxyl-proximal intein modified to be incapable of splicing. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, make and use the invention commensurate in scope with the practice of claimed methods utilizing unmodified inteins of claims 74, 76-80, 82 and 86-88, or the generation of cyclic or polymeric products of claims 81 and 89.**

This new ground of rejection is necessitated by Applicant's amendment introducing new claims 74, 76-82, and 86-89. The above limitation statement is based on teachings of the specification at page 4, lines 7-10, from line 5 at page 10 through line 9 at page 12, and at page 12, lines 19-25, which support cyclization or polymerization methods described by the new claims 74 and 82 practiced with inteins modified to be incapable of splicing but that do not suggest unmodified inteins might be used for methods of claims 74 and 82 where extracellular preparations of expressed fusion polypeptides are made according to the paragraph at lines 1-3 at page 11 of the specification. Claim 74, and claims 76-80 dependent thereon, contemplate methods of making cyclic peptides or polypeptides wherein, according to clause (a) of claim 74, both a first and a second "unmodified" intein flank a target protein in a recombinantly-expressed fusion protein. After obtaining an extracellular preparation of the expressed fusion protein intermediate according to clause (b) of claim 74, both inteins are cleaved according to clause (c) of the claim to generate a target protein having the two elements needed to form a cyclic protein: an amino-terminal cysteine and carboxyl-terminal thioester. Yet claims 74 and 76-80 also allow a cyclization method to embrace the expression of a fusion protein intermediate wherein the other terminus of either or both inteins flanking a target protein

intended for cyclization is further fused to another polypeptide, such as a binding protein to permit isolation by, e.g., affinity chromatography. No prior art teaching, including the teachings of U.S. Patent No. 5,834,247 and Telenti et al., cited above, suggests that a peptide or polypeptide destined to become a cyclic protein may be expressed as an intermediate fusion protein flanked by two unmodified inteins according to a claimed method, wherein either or both inteins are themselves flanked by a another polypeptide as disclosed by the specification and as permitted within the embrace of the claims, and avoid a splicing reaction which would change the intended target to some other polypeptide and short-circuit cyclization. The specification itself does not teach that an unmodified intein also fused to an external, flanking, peptide or polypeptide that permits isolation of the expressed fusion protein by, e.g., a binding ligand, can be used to obtain an extracellular preparation of fusion proteins suitable for cleavage to yield target proteins having the two necessary terminal elements. Instead, the specification teaches that the requisite amino-terminal cysteine and carboxyl-terminal thioester must both be formed by cleavage of the flanking inteins from the target protein if the desired target is to then become a cyclic protein. Thus the flanking inteins must be incapable of splicing *in vivo*, i.e., in a host cell prior to extracellular isolation of the fusion polypeptide, and *in vitro*, after its isolation in an extracellular preparation, prior to cleavage because splicing would make the desired target protein unavailable for cyclization.

Claim 82 and claims 86-88 dependent thereon contemplate similar methods using unmodified inteins to make polymeric proteins wherein, according to clauses (a) and (b) of claim 82, an extracellular preparation of recombinantly-expressed fusion proteins is obtained, each comprising a first and a second "unmodified" intein that flank a target peptide or polypeptide, then the inteins are both cleaved according to clause (c) of the claim to make a desired target protein having two elements needed for polymerization:

an amino-terminal cysteine and carboxyl-terminal thioester. Yet claims 82 and 86-88 also allow a method for polymerization to embrace the expression of a fusion protein intermediate wherein the other terminus of either or both inteins flanking a target protein intended for polymerization is further fused to another polypeptide, as disclosed by the specification and permitted within the embrace of the claims, such as a binding protein for isolation by affinity chromatography. Neither the specification nor any prior art teaching suggest that a peptide or polypeptide destined to become a polymeric protein may be expressed as an intermediate fusion protein flanked by two unmodified inteins by a claimed method wherein either or both inteins are flanked by another polypeptide as disclosed by the specification and permitted within the embrace of the claims.

Because the specification fails to exemplify, see pages 5-8, 13-21 and Figures 1-4, either a claimed cyclization or a claimed polymerization of target proteins, either singly or as a "plurality", using an unmodified intein, it provides no basis for extending the embrace of methods of claims 77 and 78 to the use of either an unmodified intein fused to the amino terminus of a target protein or an unmodified intein fused to the carboxyl terminus of a target protein within an expressed fusion protein whereby both inteins must be cleaved to provide a target protein's amino-terminal cysteine and carboxyl-terminal thioester required for cyclization, or for polymerization, and neither cleavage may be vitiated by an earlier splicing event.

It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (recognizing and applying the "*Forman*" factors). Cf., *Ex parte Forman*, 230

USPQ 546, 547 (Bd. Pat. App. & Int. 1986) (citing eight factors relevant to analysis of enablement). Because the prior art of record taken together with the disclosure of the specification does not suggest how the two cleavages producing a target protein with an amino-terminal cysteine and a carboxyl-terminal thioester necessary in the claimed methods might be achieved with inteins not modified to inhibit splicing, the state of the art and the level of skill in the art cannot compensate for the lack of teaching in the instant specification for the practice of methods embracing the use of unmodified inteins set forth in claims 74, 76-80, 82 and 86-88, or for the products resulting from such methods of claims 81 and 89.

**The following is a quotation of the second paragraph of 35 U.S.C. § 112:**

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

**Claims 63, 65-72 and 82-89 are rejected, the latter essentially for reasons of record under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Claim 63 is indefinite in reciting "adjacent to a coding **sequence for the specified amino acid** other than methionine" (emphasis supplied) because this addresses only an absence of specific trinucleotides, the codon "AGT" used by both eukaryotes and prokaryotes and the codon "GGT" used in some genes of gram-positive prokaryotes, as a "coding sequence" specifying methionine rather than a polypeptide coding sequence. This recitation is ambiguous because Applicant does not intend that a coding sequence for a "target protein" have but a single codon, but intends that a nucleic acid sequence encoding a fusion protein have "an intein-encoding nucleic acid sequence adjacent to the region of the nucleic acid sequence encoding the amino-terminus of a target protein wherein the amino-terminal amino acid is not a methionine". Claim 64 is included in this rejection because it depends from claim 63 but does not otherwise resolve its ambiguity.

Claim 65 is indefinite in reciting "a method for ligating a **plurality** of target proteins" (emphasis supplied) because the specification does not disclose that a "plurality" - i.e., a multiplicity of polypeptides that may exceed two - can be ligated to form a product that comprises only a first and a second target polypeptide as recited in the terminal clause of claim 65. Instead it discloses that a first and a second target polypeptide can be ligated to form a product that comprises only a first and a second target polypeptide. Claims 66-72 are included in this rejection because they depend from claim 63 but fail to resolve its ambiguity. Amending claim 65 to delete the words "a plurality of" will overcome this aspect of the rejection affecting claims 65-72.

Claims 82 and 88 are both indefinite in reciting a method for polymerizing a plurality of target proteins "of one **type**" (emphasis supplied) because the specification does not identify different types of target proteins and because neither the artisan nor the public reading the specification can determine how one "type" of protein might differ from another "type" of protein so that the "one type" apparently required by the claim preamble is used in the method. In addition it is not clear whether or not the individual exemplars of a "plurality" - i.e., a multiplicity of polypeptides that may exceed two - of target proteins "of one type" may differ in any respect, e.g., in primary sequence, in post-translational modification, or in chemical modification. While the artisan and the public reading the specification may not determine what is intended by a "plurality . . . of one type", the specification clearly shows, page 4 at lines 7-10, that Applicant did not intend that proteins used in a method of polymerization differ in any way, however slight and whether or not taken as a "plurality". The specification instead discloses a method requiring "a single protein having both a C-terminal thioester and a specified N-terminal amino acid . . . for the creation of cyclic or polymerized proteins." Claims 83-87 are also rejected because they depend from claim 82 but fail to clarify its ambiguities.

Amending both of claims 82 and 88 to recite "a method for polymerizing **a** target protein" (emphasis supplied) will overcome this aspect of the rejection affecting claims 82-88.

Claims 72, 79 and 87 are each indefinite in reciting "at least one **cell type** selected from the group consisting of . . . a mammalian **cell type**" because the specification discloses no cell "types" and artisan and the public seeking to distinguish a "type" of, e.g., a mammalian, cell suitable for a claimed method from a "type" of cell unsuitable for a claimed method cannot know the basis for such distinction. Instead, the specification discloses, at page 3, lines 1 and 2, that plasmids comprising nucleic acid sequences used in a claimed method permit "expression" of a precursor fusion protein in "a host cell, such as [a] bacterial, yeast, or mammalian **host cell**" (emphasis supplied) and further discloses plant and insect host cells at page 10, lines 16 and 17. Amending claims 72, 79 and 87 to recite " capable of expression in **a host cell** selected from the group consisting of **a** bacterial, **a** yeast, **an** insect, **a** plant, and **a** mammalian **host cell**" (emphases supplied) will overcome this aspect of the rejection of these claims.

*Claim Rejections - 35 USC §§ 102 and 103*

**The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:**

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

**The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:**

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a

whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. §§ 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

**Claim 63 is rejected under 35 U.S.C. § 102(a) as anticipated by Telenti et al., 1997, of record.**

New claim 63 necessitates this new ground of rejection. Telenti et al. disclose the preparation of polypeptides having a specific, therefore specified, amino-terminal amino acid other than methionine upon the induced cleavage of an amino-proximal intein comprised together with a target polypeptide within a fusion polypeptide prior to cleavage. See entries of lateral results for "C-terminal cleavage" in the vertical columns designated "RT for 5 days" in Table 1 at page 6380, where a threonine is present at the amino terminus of the paramyosin C-terminal cleavage product - depicted as the "P" region in the fusion polypeptide "MIP" - resulting from induced cleavage of the MIP fusion polypeptide and a threonine is also present at the amino terminus of the native 64-amino acid carboxyl-proximal GyrA extein region - depicted as the "E" region in the "MIEP" fusion polypeptide and as the second "E" region in the "MEIEP" fusion polypeptide. Thus threonine was twice selected, hence specified, as the amino terminal amino acid of an intein C-terminal cleavage product.

**Claim 63 is rejected under 35 U.S.C. § 102(e) as anticipated by Comb et al., U.S. Patent No. 5,834,247, of record.**

New claim 63 necessitates this new ground of rejection. Comb et al. '247 explicitly teach the subject matter of claim 63 at col. 42, lines 10-47.

**Claim 81 is rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Albericio et al., U.S. Patent 5,777,077, made of record herewith.**

Because the process by which a product of the new claim 81 is made is described by the new claim 74, Applicant's amendment necessitates this new ground of rejection. Neither claim 81 nor the specification require that a product of the process of claim 74 comprising naturally-occurring amino acids, including at least one cysteine, linked by native peptide bonds that is a cyclic protein have a particular length or size. Albericio et al. disclose, at cols. 1-13 and 15-16, the use of manual and automated allyl deprotection for the solid-phase synthesis of cyclic peptides wherein naturally-occurring amino acids, including cysteine, are linked exclusively by native peptide bonds, termed, col. 2 at line 62, "head-to-tail cyclic peptides", where, col. 5 at lines 29-32, "allyl protecting groups can be attached to a sulfur atom present in the sulfhydryl side-chain functional group of cysteine . . ." to allow inclusion of cysteine in such a cyclic peptide. The disclosure of Albericio et al. is considered to anticipate claim 81 because it enables and discloses the preparation of cyclic peptides of any size comprised entirely of naturally-occurring amino acids, including cysteine, joined exclusively by native peptide bonds, particularly where the disclosure of Albericio et al. is as extensive as that of the instant application which discloses no particular cyclic protein product. In the alternative, Albericio et al. are considered to have rendered the subject matter of claim 81 obvious to one of ordinary skill in the art at the time the invention was made because they teach such an artisan how to prepare a cyclic peptide of any size entirely comprising naturally-occurring amino acids, including cysteine, joined exclusively by native peptide bonds and also provide motivation to make such cyclic peptides for "research or therapeutic purposes", at col. 1 at lines 14-15, a motivation commensurate with that present in the instant specification.

**Claim 89 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Stevens, U.S. Patent 6,217,881, made of record herewith, in view of Albericio et al., cited above.**

New claim 89 necessitates this new ground of rejection. Stevens teaches, col. 45 at lines 57-65, the head-to-tail polymerization with native peptide bonds of multimers of peptides, comprising naturally-occurring amino acids, in amino sequences of regions of human chorionic gonadotrophin hormone that comprise a cysteine, including those set forth in, e.g., Structures IV, V, VIII, VIIIa, X, XI, XII, and IX at cols. 21-22, in order to prepare a topically immunogenic contraceptive compound. The teachings of Alberico et al. of a method of making peptides comprising naturally-occurring amino acids, including cysteine, linked exclusively by native peptide bonds is taken as before, and the preliminary teachings of Alberico et al. at col. 6, lines 25-33, now emphasized, i.e., the preparation of linear peptides of any desired sequence of naturally-occurring amino acids that need not be subsequently cyclized. It would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the method of Alberico et al. in preparing the polymeric immunogenic proteins of Stevens, modified by excluding the optional process of cyclization, because Alberico et al. provide a suitable technology to make polymeric immunogenic proteins that Stevens teaches to be useful as polymers linked by native peptide bonds.

**Claims 64, 65 and 69-73 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Comb et al., U.S. Patent No. 5,834,247, of record, in view of any of Kent et al., U.S. Patent No. 6,184,334, or Tam, U.S. Patent No. 6,310, 180, or Canne et al., U.S. Patent No. 6,326,468, all of record.**

New claims 64, 65 and 69-73 necessitate this new ground of rejection. Comb et al. '247 teach a method for producing a desired, or target, polypeptide that is expressed in two segments in different host cells, thus inherently requires a two-plasmid system, wherein one host cell recombinantly expresses a first modified protein comprising the amino-proximal portion of the desired target protein fused at its carboxyl-terminus to a modified intein, which is an amino-proximal region of a truncated intein, and the other host cell recombinantly expresses a second modified protein which is the carboxyl-

proximal portion of the desired target protein fused at its amino-terminus to a modified intein, which is a carboxyl-proximal region of a truncated intein, and the two fusion proteins are isolated from their different host cells and incubated together to facilitate release of both modified intein portions of the separate fusion proteins and the formation of a "ligated target protein". See col. 16, line 49 through col. 17, line 51, and particularly see col. 16 at line 59 stating, "This results in a ligated target protein". Comb et al. '247 further teach, see col. 17 at lines 52-67, that the fusion polypeptides comprising either segment of the desired target protein and the proximal modified inteins may further comprise a binding protein fused to the other terminus of the modified intein to facilitate separate isolation of either or both segments of the target protein present within their respective fusion polypeptides. Comb et al. '247 also teach that intein cleavages from either fusion polypeptide may occur "in trans", i.e., separately, at col. 18, lines 1-41, to release an adjacent modified intein from either segment of the target protein where the opposite, free, segment of the target protein is added as a "peptide" to the isolated fusion polypeptide that either comprises the amino-proximal portion of the target protein, lines, at lines 13-24, or the carboxyl-proximal portion of the target protein, at lines 25-41. Comb et al. '247 explicitly teach that a free, carboxyl-proximal, segment of a target protein added to an incubation with a fusion polypeptide comprising a modified intein fused to the carboxyl-terminus of the amino-proximal segment of the target protein may advantageously have an amino-terminal cysteine at col. 18, line 22, so that ligation may proceed. See also, Fig. 1 of Comb et al. '247, depicting cysteine as the amino-terminal amino acid of exteins that flank native yeast and mycobacterial intein carboxyl termini. Thus, Comb et al. '247 teach the *in vitro* production of a carboxyl-proximal segment of a desired target protein by temperature-induced cleavage of a fusion protein comprising an adjacent, amino-proximal, intein, and clearly suggest that cysteine is a suitable

amino-terminal amino acid for such a product, rendering the subject matter of claim 64 obvious to one of ordinary skill in the art at the time the invention was made, and clearly suggest that such a free carboxyl-proximal target protein segment, advantageously having an amino-terminal cysteine, may be ligated with an amino-proximal target protein segment fused to a carboxyl-proximal intein in an expressed fusion polypeptide to produce a desired target protein.

Comb et al. '247 explicitly teach the entirety of clauses (a) and (d), and portions of clauses (c) and (f), of claim 65 as well as limitations of clauses 69-72 and the entirety of clause (a)(i), as well as part of clause (b), of claim 73, in Examples 18-20 at cols. 73-80. Comb et al. '247 explicitly teach the entirety of claim 63, the entirety of clause (b) of claim 65, and parts of clauses (c), (e), and (f) of claim 65, as well as parts of clauses (a)(ii) and (b) of claim 73, at col. 42, lines 10-47. Comb et al. '247 do not explicitly teach that the carboxyl-proximal segment of a desired target protein should be recombinantly expressed in a fusion polypeptide comprising a modified intein fused to its amino terminus in order to be cleaved *in vitro* from the intein and incubated with the amino proximal portion of the desired target protein having a C-terminal thioester according to Example 20 of Comb et al. '247, but they nonetheless teach the *in vitro* production of a carboxyl-proximal segment of a desired target protein by temperature-induced cleavage from an adjacent, amino-proximal, intein in a fusion protein, suggest that cysteine is a suitable amino-terminal amino acid for such a product, and suggest that such a product may be used in a ligation reaction. Comb et al. '247 teach the requisite parts of the claimed methods separately, but do not add them so as to practice methods of claims 65 and 69-73.

The teachings of each of Kent et al., Tam, and Canne et al., made of record in the Office communication mailed April 23, 2002, are now combined with teachings of Comb

et al. '247 of recombinant preparation of the requisite components for a claimed method to show that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use those components separately taught by Comb et al. '247 in the methods of ligation now claimed herein. As discussed at pages 4-6 of the Office communication mailed April 23, 2002, each of Kent et al., Tam, and Canne et al. teach the *in vitro* ligation of different segments of a desired protein by incubating the amino-terminal segment having a carboxyl-terminal thioester and the carboxyl-proximal segment having an amino-terminal cysteine. Neither the amino-proximal segments nor the carboxyl-proximal segments of the various desired proteins ligated by each of Kent et al., Tam et al., and Canne et al. were previously fused to inteins and comprised within fusion polypeptides recombinantly expressed in host cells from fusion polypeptide-encoding sequences present in separate plasmids, but each of Kent et al., Tam, and Canne et al. teach that either segment of a polypeptide ligated in their methods may be "recombinantly expressed", see col. 5, lines 27-31 of Canne et al., or "derived from . . . recombinant DNA methodologies", see col. 41, lines 54-57 of Tam, or "expressed by standard rec[ombinant]DNA means", see the paragraph spanning cols. 8-9 or Kent et al.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to practice the methods of claims 65 and 69-73 by substituting, in each of the ligation methods of Kent et al., Tam or Canne et al., both (1) an amino-proximal segment of a desired polypeptide having a carboxyl-terminal thioester prepared by thiol-reagent induced cleavage of a modified intein fused at its amino terminus to the carboxyl terminus of the amino-proximal segment of the desired polypeptide, particularly where Comb et al. '247 explicitly teach that this should be done to prepare a suitable amino-proximal segment of a desired polypeptide for *in vitro* ligation to a second, carboxyl-proximal, peptide or polypeptide having an amino-terminal cysteine and, (2) a

carboxyl-terminal portion of a desired polypeptide having an amino-terminal cysteine prepared by temperature-induced cleavage of either a modified or an unmodified intein fused at its carboxyl terminus to the amino terminus of the carboxyl-proximal segment of the desired polypeptide, because each of Kent et al., Tam or Canne et al. suggest that a recombinantly-expressed polypeptide may be such a carboxyl-proximal segment to be ligated to produce a desired polypeptide and because Comb et al. '247 teach how to make such a carboxyl-proximal segment, that may be ligated to produce a desired polypeptide, by recombinantly expressing it as the carboxyl-proximal portion of a fusion polypeptide wherein it is fused at its amino terminus to the carboxyl terminus of a modified or unmodified intein and then cleaved from the intein *in vitro* by incubation at a temperature capable of inducing such cleavage, and also because Comb et al. '247 teach that cysteine is a preferred amino-terminal amino acid for such a segment of a protein that may be ligated to an amino-proximal segment of a desired polypeptide *in vitro* to produce the complete, integral, desired polypeptide.

*Conclusion*

Claim 90 would be allowable if amended to avoid the objection stated above. While claims 74-80 and 82-88 are free of the prior art of record herein, which neither discloses nor suggests the claimed methods, claims 79, 82, 87 and 88 must be amended to overcome the rejections stated hereinabove under the first and second paragraphs of 35 U.S.C. § 112 in order to describe allowable subject matter.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is 571.272.0933. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached at 571.272.0928. The fax phone numbers for all communications for the organization where this application or proceeding is assigned remains 703.872.9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571.272.1600.

William W. Moore
March 4, 2004

NASHAAT T. NASHED PHD.
PRIMARY EXAMINER